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EXAMINER

LEWIS, PATRICK T

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in the reply filed on September 13, 2007 is acknowledged. The requirement was made FINAL in the Office Action dated September 27, 2007.
2. Claims 11, 15, 19, 25-26, 28-29 and 37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant's Response Dated December 27, 2007

3. Claims 1-4, 11, 15, 19, 25-26, 28-29 and 37 are pending. An action on the merits of claims 1-4, 11, 15, 19, 25-26, 28-29 and 37 is contained herein below.
4. The objection to claim 10 has been rendered moot in view of applicant's amendment dated April 25, 2008.
5. The rejection of claims 1-4, 9-10 and 16 under 35 U.S.C. 112, first paragraph, has been rendered moot in view of applicant's amendment dated April 25, 2008.
6. The rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Brask et al. Journal of peptide Science (2000), Vol. 6, pages 290-299 (Brask) and Nefzi et al. Tetrahedron Letters (1995), Vol. 36, pages 229-230 (Nefzi) in combination is maintained for the reasons of record as set forth in the Office action dated September 27, 2007.

7. The rejection of claim 9 under 35 U.S.C. 103(a) as being unpatentable over Brask et al. Journal of peptide Science (2000), Vol. 6, pages 290-299 (Brask) and Nefzi et al. Tetrahedron Letters (1995), Vol. 36, pages 229-230 (Nefzi) in combination has been rendered moot in view of applicant's amendment dated April 25, 2008.

Rejections of Record Set Forth in the Office Action Dated September 27, 2007

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

9. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brask et al. Journal of peptide Science (2000), Vol. 6, pages 290-299 (Brask) and Nefzi et al. Tetrahedron Letters (1995), Vol. 36, pages 229-230 (Nefzi) in combination.

Claims 1-4 are drawn to a maleimide cluster comprising at least one core carbohydrate molecule wherein at least two or more maleimides are attached to the core and optionally comprising a protein.

Brask teaches multifunctional, topological template molecules such as linear and cyclic peptides have been used for the attachment of peptide strands to form novel protein models (Abstract). The concept of carbohydrates as templates for de novo design of potential protein models has been previously described and these novel chimeric compounds were termed carbopeptides. (page 290) To bypass the problematic folding step of linear polypeptides, Mutter and coworkers have suggested a template-assembled synthetic proteins (TASP) concept which relies on a multifunctional topological scaffold or template, which enhances the spatial accommodation of the

peptides. Carbohydrates are promising candidates for templates for the display of functional groups due to their inherent multifunctionality, the relative rigidity of ring forms, ease of regioselective chemical manipulations, and access to stereoisomers of mono- and disaccharides (page 291). The preparation of carbopeptides by oxime ligation is shown in Figures 2-5. In a model study, 2,4-dimethoxybenzaldehyde was coupled to methyl 2,3,4,6-tetra-O-Aca- α -D-Galp (7) at room temperature (page 296).

Brask differs from the instant invention in that Brask does not teach a TASP containing maleimide functions; however, it would have been obvious to one of ordinary skill in the art at the time of the invention to do so in view of the teachings of Nefzi.

Nefzi teaches a method of chemoselective ligation for TASP synthesis using the maleimide function, which is known to react rapidly and rather selectively with thiols (page 229). This should allow for the condensation of peptides containing a thiol group to template molecules containing the maleimide function. Applicant's attention is directed to Scheme 1 wherein Nefzi shows a maleimide function covalently attached to a template which is then reacted with a thiol-containing peptide.

It would have been obvious to one of ordinary skill in the art at the time of the invention to attach peptides to a maleimide function covalently linked to a template. One would have been motivated to incorporate a maleimide function because they are known to react rapidly and rather selectively with thiols. It would have also been obvious to one of ordinary skill in the art to select a monosaccharide as the template. As taught by Brask, carbohydrates are promising candidates for templates for the display of functional groups due to their inherent multifunctionality, the relative rigidity of

ring forms, ease of regioselective chemical manipulations, and access to stereoisomers of mono- and disaccharides.

10. Applicant's arguments filed April 25, 2008 (December 25, 2007 have been fully considered but they are not persuasive. Applicant argues that Brask requires linkers in its synthetic proteins in order to create moveable arms within the final structure. Applicant contends that flexibility is an important characteristic of the Brask molecules which is in stark contrast to the rigid structure of the molecules described in Nefzi. Applicant further asserts that if the carbohydrate core, with or without movable arms, of Brask is introduced into the Nefzi structure, then the required rigidity of the Nefzi structure is lost.

The examiner respectfully disagrees with applicant's assertions and characterization of the prior art. Brask and Nefzi both employ Template Assembled Synthetic Proteins (TASP) to bypass the so-called protein folding problem. In this approach, peptide blocks with inherent secondary structure are attached to a topologically defined template, which promotes their folding into a distinct tertiary structure. Neither Brask nor Nefzi teach direct attachment of the peptide to the "template". Brask teaches the use of a "linker" to attach the peptide to the "template". Nefzi teaches the attachment of the peptide to the "template" by using four maleimide functions (a "linker").

Although Nefzi describes the use of generic "templates", Brask teaches that carbohydrates are promising candidates for templates for the display of functional groups due to their inherent multifunctionality, the relative rigidity of ring forms, ease of

regioselective chemical manipulations, and access to stereoisomers of mono- and disaccharides (page 291). As discussed by Brask, the development of techniques for chemoselective ligation of unprotected peptide segments has significantly extended the reach of synthetic peptide chemistry. Common to these methods is the chemoselective reaction of two mutually reactive functionalities, one on each segment. Some methods rely on the formation of a non-natural bond at the site of ligation, this includes oxime and hydrazone ligations. With aldehydes and ketones oximes are formed which are stable under neutral to mildly acidic conditions. Other chemoselective reactions are thioether and thioester ligations, based on reactions between a thiol or thioacid nucleophile and a bromoacetyl moiety.

Thus, the selection of appropriate functionalities to attach the “template” and peptide would have been well within the purview of the skilled artisan at the time of the instant invention. Nefzi teaches a method of chemoselective ligation for TASP synthesis using the maleimide function, which is known to react rapidly and rather selectively with thiols (page 229). This should allow for the condensation of peptides containing a thiol group to template molecules containing the maleimide function. Applicant’s attention is directed to Scheme 1 wherein Nefzi shows a maleimide function covalently attached to a template which is then reacted with a thiol-containing peptide. Simple substitution of one known element (i.e., a specific “linker” or “template”) for another to obtain predictable results renders the instant invention obvious in view of the teachings of the prior art.

Conclusion

11. Claims 1-4, 11, 15, 19, 25-26, 28-29 and 37 are pending. Claims 1-4 are rejected. Claims 11, 15, 19, 25-26, 28-29 and 37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. No claims are allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Dr. Patrick T. Lewis/
Primary Examiner, Art Unit 1623

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